Respiratory Medicine (2007) **101**, 1265–1276

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# Guidelines of the French Speaking Society for Chest Medicine for management of malignant pleural mesothelioma ☆

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Received 29 June 2006; accepted 16 October 2006
Available online 29 November 2006

**KEYWORDS**
Pleura;
Mesothelioma;
Guidelines;
Asbestos

**Summary**
Previously considered as a rare tumor, malignant pleural mesothelioma (MPM) has become a very important public health issue. In fact, MPM is a tumor with a poor survival, and its incidence is expected to continue to increase for at least the next 10 years. Asbestos exposure is the main factor involved in MPM pathogenesis. The diagnosis of MPM may be difficult because of differential diagnosis such as pleural benign disease induced by asbestos exposure or pleural metastasis of adenocarcinoma. Management of patients with MPM also remains complicated because they are often referred for evaluation late in the evolution of the disease. Moreover, MPM exhibits a high resistance to radiotherapy and chemotherapy; only few patients are candidates for radical surgery. New therapeutic strategies such as gene or cell therapy are still on clinical trial. Therefore, an optimal treatment of MPM is not clearly defined yet, despite the introduction of recent drugs.
Between April 2005 and January 2006, the French Speaking Society for Chest Medicine (SPLF), in collaboration with other French scientific societies, brought together experts on mesothelioma to draw up recommendations in order to provide clinicians with clear, concise, up-to-date guidelines on management of MPM, presented in this report.


## Introduction

Previously considered to be rare, malignant pleural mesothelioma (MPM) is a highly aggressive tumor that has become a very important issue over recent years.[1] Asbestos exposure is the main factor involved in pathogenesis, which can explain the rise in incidence of MPM since the 1960s.[2]

☆Funding source: French Speaking Society for Chest Medicine (Societe de Pneumologie de Langue Française, SPLF).

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doi:10.1016/j.rmed.2006.10.018

Despite the prohibition of asbestos use in France in 1997, as in most other developed countries, the number of MPM cases is expected to continue to rise for at least the next 10 years. In addition, asbestos is still widely used in many parts of the world, notably in emerging countries such as China, India or Brazil, and in less-developed nations.[1] The diagnosis of MPM is difficult because the disease may occur up to 30–40 years after asbestos exposure, and the differential diagnosis on pleural biopsy between MPM and pleural benign disease or metastasis of adenocarcinoma may be difficult in some cases, even with the use of immunohistochemistry.[3] Since patients with MPM have a poor outcome and an optimal treatment is not clearly defined,[4,5] MPM will remain a major public health problem for many years.

In order to address this issue, the French Speaking Society for Chest Medicine (SPLF), in collaboration with the French Societies of Pathology (SFP), of Thoracic and Cardiovascular Surgery (FSTCVS) and of Occupational Medicine (SFMT), brought together experts on mesothelioma from the four different Societies between April 2005 and January 2006 to draw up recommendations in order to provide clinicians with clear, concise, up-to-date guidelines on management of MPM. After a public discussion during the 10th CPLF Meeting in Nice on 27 January 2006, these recommendations were first published in French,[6] then translated in the present publication. The choice of an expert conference rather than a consensus conference was made because of the limited amount of information on mesothelioma currently available in the literature. Practical questions relating to MPM were raised by a scientific committee of the SPLF. A systematic analysis of the literature was realised using the following databases: Medline (National Library of Medicine, USA), Embase (Elsevier, Netherlands), Cochrane Library (Great Britain), National Guideline Clearinghouse (USA), HTA Database (International Network of Agencies for Health Technology Assessment—INAHTA), BDSP (Public Health Database, Rennes, France), NIH database (USA), International Pleural Mesothelioma Program—WHOLIS (WHO Database). Each recommendation was graded by the experts, based on the official proposal for evidence-based medicine, provided by the French government's High Authority for Health (HAS) (see Table 1). Each recommendation was voted by all experts: if less than 85% of the experts were in total agreement with one proposal, the corresponding recommendation was modified after a new discussion.

These guidelines do not answer to all unresolved questions in the management of MPM. In fact, the literature is really poor on many aspects of mesothelioma. In particular, the question on the role of treatment of mesothelioma was not perfectly addressed as there is no real publication fully answering to this point yet.[11] However, several studies have shown that current doublets of chemotherapy can improve the survival of MPM in comparison to single monochemotherapy[7,8] without altering the quality of life of patients.[9] Moreover, a small recent trial study was in favour of an early use of chemotherapy to provide an extended period of symptom control and a trend to survival advantage.[10]

In conclusion, the Expert Conference organised by the SPLF provided guidelines on MPM management for clinicians and patients, including the latest diagnostic or therapeutic tools available in 2005. This Conference also aimed at stimulate collaborations between the different actors involved in MPM management, including research laboratories.

**Table 1** Official proposal for evidence-based medicine, provided by the French government's High Authority for Health (HAS) in order to give a grade to the recommendations by the experts.

| Scientific level of proof | Recommendation grade |
|---|---|
| Level 1<br>• Randomised comparative trials with high power<br>• Meta-analysis of randomised comparative trials<br>• Analysis of decision based on well-conducted studies | A. Established scientific proof |
| Level 2<br>• Randomised comparative trials with low power<br>• Non-randomised, well-conducted comparative studies<br>• Cohort studies | B. Scientific presumption |
| Level 3<br>• Case control studies | C. Low level of scientific proof |
| Level 4<br>• Comparative studies with significant bias<br>• Retrospective studies<br>• Case reports<br>• Observational studies (cross-sectional, longitudinal) | |

## Question 1: How is exposure to asbestos evaluated and how is the at-risk population identified?

### Question 1.1: What are the risk factors associated with malignant pleural mesothelioma (MPM), which enable at-risk populations to be identified?

To date, two risk factors have been clearly established for MPM: exposure to asbestos and to erionite. Other risk factors for MPM have also been proposed, namely exposure to other mineral fibres (particularly refractory ceramic fibres), iodising radiation and SV40 virus. Tobacco exposure, on the other hand, is known to not play a role in the development of mesothelioma.

- It is widely accepted that asbestos is the main aetiological agent of MPM. Although a dose–effect relationship has been demonstrated, it has not been possible to identify a threshold cumulative exposure level below which there is no increased risk of developing the disease. It is therefore recommended that individuals who have been exposed to asbestos are targeted as the main population at risk (A).

The risk of mesothelioma attributable to asbestos differs markedly between men and women. To date, the reason for this difference is unclear. It has been suggested that this might result purely from inaccurate identification of asbestos exposure, notably in situations of low and environmental exposure.

- Further investigations into other potential aetiological factors are recommended, particularly in females because of their lower frequency of exposure to asbestos (A).

Genetic factors, which increase susceptibility, may contribute to the development of mesothelioma. This hypothesis is based essentially on the observation of familial cases of mesothelioma. Nevertheless, no candidate gene has been identified to date which predisposes an individual to mesothelioma.

### Question 1.2: What methods are available to evaluate exposure to asbestos?

The probability of mesothelioma occurring after exposure to asbestos depends on two factors:

- The time since the first asbestos exposure.
- The cumulative dose of asbestos, expressed as fibres/ml air $\times$ number of years of exposure. This formula takes into account the number of episodes of exposure, each episode being evaluated as the product of the mean extent of exposure during the episode and the duration of the episode.

Two methods can be used to estimate these two parameters: occupational and environmental case histories, and biometrology. In practice, it is important to define the methods used to evaluate exposure in the following three circumstances:

- *Compensation*: in contrast to previous regulations, current French regulations do not require exposure to be determined in a precise manner.
- *Screening*: should only be carried out on individuals with known exposure.
- *Epidemiological studies*: classification errors can lead to either systematic bias (overestimation of exposure for cases compared to controls), or a tendency to underestimate the real risk (errors equally distributed among cases and controls).

The choice of tools for evaluating exposure will depend on their precision and relevance for each type of study.

It is not possible to establish an exhaustive list of occupations or work sectors associated with an increased risk of MPM. Nevertheless, several occupations are clearly associated with a reproducible relative risk greater than two. This is the case, for example, for plumbers/pipe fitters, electricians, carpenters–cabinetmakers and other occupations in the construction industry. In addition, several other work sectors have been associated with an increased risk of mesothelioma in several studies. These include shipyards, industries producing and manufacturing articles made of asbestos and the construction industry in general. However, the list of risk situations should not be restricted to these occupations or work sectors. Although data in the literature suggest that chrysotile asbestos and amphibole asbestos may be associated with different degrees of pleural carcinogenicity (the latter having higher potency), current exposure questionnaires do not enable exposure to these two types of fibres to be distinguished.

- Occupational and environmental anamnesis is the fundamental tool to determine exposure to asbestos. This has to be used systematically for every patient with MPM (A).
- The advice of specialised consultations for Occupational Medicine should be sought when exposure to asbestos is not obvious (advice of experts).
- The occupational activity (sector of work and occupation) considered to be the possible cause of exposure to asbestos should figure systematically in the patient's case notes (advice of experts).
- The clinician should refer to the lists of work sectors, occupations and occupational activities linked to asbestos exposure to evaluate the importance of exposure (for example: http://www.sante-securite.travail.gouv.fr/mediatheque/pdf/medecin%20travail.pdf) (C).

Biometrology consists of the measure of asbestos (asbestos bodies by optical microscopy, or asbestos fibres by transmission electron microscopy, with analysis of chemical elements) in biological specimens (lung tissue, bronchoalveolar lavage fluid, sputum). The technique enables subjects with an abnormally high level of asbestos retention in the respiratory tract to be identified and identifies abnormal previous exposure, irrespective of its origin.

Carrying out biometrology (search for asbestos bodies in biological specimens) is not an essential part of current

clinical practice (diagnosis and medico-legal compensation) with respect to MPM. However, biometrology (optical or electron microscopy) is still useful for research and aetiological studies (notably determination of the type of asbestos retained).

Negative biometrology testing (a level of retention of asbestos bodies seen by optical microscopy, or fibres identified by electron microscopy, below thresholds for abnormal retention with respect to the general population) does not eliminate the possibility of sufficient exposure to induce mesothelioma.

- From the viewpoint of identifying populations at risk for mesothelioma, likely to be included in screening programmes, the only possible biometrology method is the detection of asbestos bodies in sputum (advice of experts).
- Nevertheless, it has not been demonstrated to date whether biometric examination for asbestos bodies in sputum provides additional information compared to thorough anamnesis for the identification of exposure to asbestos in the general population (advice of experts).

### Question 1.3: Is there a place for screening for mesothelioma? If so, what tools should be used?

For a screening programme to be justified, it is necessary that detection of the disease can be followed by effective intervention. It is also necessary to demonstrate the efficacy and harmlessness of the screening programme, including all the steps involved in early diagnosis and treatment in identified patients (for interventions at the individual patient level) and all prevention methods taken. As any health-related procedure, the efficacy of a screening programme is defined by a higher benefit/risk ratio for a population undergoing screening than for a population not being screened.

During a previous French consensus conference in 1999, which focussed on the development of a clinical supervision programme for individuals exposed to asbestos, the panel concluded that the medico-social impact of screening for mesothelioma should be evaluated.

Taking into account the data currently available on MPM (prevalence, prognosis, therapy), and the performance (sensitivity, specificity) of available screening methods (thoracic imaging, biological markers), the value of a screening from a medical and public health viewpoint has not been demonstrated to date.

Two types of approach can be considered: thoracic imagery and biological markers.

- Chest conventional radiograph has low sensitivity for the detection of weak or moderate pleural effusions
- Ultra-sound is a simple and sensitive technique to detect pleural effusion but does not offer complete assessment of the pleural cavity
- Pleural effusion and pleural thickening are the two signs which can suggest the presence of mesothelioma on chest computed tomography scanning (CT scan)
- Magnetic resonance imaging (MRI) and [$^{18}$F]-fluorodeoxyglucose positron emission tomography (PET) are currently not used as screening techniques, due to their high cost and limited availability.

Post-occupational monitoring, which has been proposed for individuals with previous exposure to asbestos, will increasingly include an initial chest CT scan starting at 50 years of age, using a standardised protocol for examination and interpretation. If pleural effusion is identified with CT scan, a systematic diagnostic procedure can be proposed, consisting of thorascopy with pleural biopsies. In contrast, complementary strategies for investigating pleural thickening identified on CT scan have not yet been validated.

- When an abnormality is identified by CT scan, it is important that an additional diagnostic strategy of investigation be proposed and evaluated in order to determine the value of biological markers, PET, MRI and the frequency of these examinations (A).

The value of using serological markers for proliferation of tumoral mesothelial cells is being reinvestigated, following the recent demonstration of an increase in levels of soluble mesothelin-related peptides (SMRP) or osteopontin in the serum of patients with MPM. Nevertheless, the amount of data available is limited and does not yet permit satisfactory evaluation of the sensitivity (as a function of cell differentiation and proliferation) or specificity (presence or absence of the marker in other cancers). The value of these markers for screening should be separated from their potential value in initial diagnosis and/or monitoring the outcome of mesothelioma.

- The performance of biological markers of MPM has not been evaluated sufficiently to date. Therefore, it is recommended that such biological markers should not be used for screening for MPM, even in populations exposed to asbestos, outside specific research programmes (A).

## Question 2: What are the diagnostic criteria for MPM?

### 2.1. Diagnostic methods

**Question 2.1.1: Are there any clinical diagnostic criteria?**
The clinical manifestations of MPM are not specific and usually appear late at an advanced stage in the course of the tumour. Clinical signs suggesting a diagnosis of MPM include chest pain, thoracic retraction or a unilateral thoracic mass in patient with a past history of asbestos exposure.

- It is recommended to not base a diagnosis of MPM on clinical criteria (A).

**Question 2.1.2: Are there any imaging criteria for MPM diagnosis?**
Conventional chest radiograph is only abnormal in the advanced stages of MPM with, in the majority of cases, a

non-specific, unilateral, pleural effusion. Chest radiograph is relatively cheap but its diagnostic accuracy (sensitivity, specificity) is poor.

- It is recommended to not use chest radiograph to assess a diagnosis of MPM (A).

Chest high-resolution CT scan is a key imaging procedure for the diagnosis of MPM. It is unable for definitive diagnosis, but certain features, such as the presence of pleural diffuse thickening or mass with thickening of interlobular fissures, are highly suggestive of MPM. However, the value of CT scan in patients with an abundant pleural effusion is poor (non-specific feature). CT scan is also relevant, before a thoracoscopy, for the evaluation of tumour extension to the chest wall, pericardium, diaphragm, mediastinal structures or locoregional lymph nodes, and the detection of infra-diaphragmatic invasion or metastases. CT scan is the cornerstone for longitudinal follow-up of patients.

- It is recommended that follow-up be carried out, after removal of pleural effusion, by a chest and abdominal multidetector (MD) CT scan with multiplaner reformation, for diagnosis and staging of MPM (A).

In contrast to CT scan, MRI is not systematically performed. Although MRI is not relevant for the diagnosis of mesothelioma, it can be helpful for the determination of the extent of the tumor to the local organs (diaphragm, mediastinum, chest wall). This technique is usually reserved for patients who are candidates for radical surgery. The diagnostic performance of MRI for the determination of the tumor extension is considered to be better compared to CT scan. Nevertheless, no study to date has assessed the effectiveness of MD CT scan for the MPM staging. Comparative studies during surgery revealed the limits of MRI for the disease staging. In particular, as for CT scan, the N and T stage disease can be underestimated in patients undergoing surgery.

- It is recommended that thoracic MRI is not systematically performed for the diagnosis of MPM (C).

(PET usually shows a hypermetabolism of pleural mesothelioma, metastatic adenopathy and metastasis. The diagnostic relevance of these features is considered as poor. The place of PET combined with CT scan and its exact role in the diagnosis of MPM are unknown.

It is recommended that PET is not performed systematically for the diagnosis of MPM (advice of experts). However, the value of PET combined with CT scan in the diagnosis of MPM requires further evaluation.

**Question 2.1.3: Are there any diagnostic criteria linked to the analysis of pleural fluid?**
Examination of pleural fluid is insufficient for the unequivocal diagnosis of MPM. No discriminant pleural fluid marker (such as hyaluronic acid) has been yet established. Nevertheless, the value of the level of SMRP and osteopontin measured in the pleural fluid should be evaluated.

- It is recommended to not base a diagnosis of MPM on the analysis of soluble markers in the pleural fluid (A).

**Question 2.1.4: What is the place of transparietal biopsies?**

- Transparietal biopsies with or without CT scan or ultrasound guidance are not recommended for the diagnosis of MPM except in patients for whom thoracoscopy is contraindicated (A).

**Question 2.1.5: What is the place of lymph node biopsies?**
Histopathology can be confusing between MPM and lymphatic drainage of normal mesothelial cells originating from an effusion. In a few cases, a diagnosis of MPM can be obtained by a biopsy of superficial adenopathy, but it is crucial to seek the advice of a panel of experts.

- It is recommended to not base a diagnosis of MPM on lymph node biopsies without validation by a panel of experts in pathology (A).

**Question 2.1.6: Are there any biological diagnostic markers of MPM?**
No tumor marker (including hyaluronic acid) can currently be considered reliable. The level of SMRP in blood or pleural fluid appears promising, since SMRP levels appear to correlate with tumor mass. However, the value of SMRP and osteopontin in the diagnosis of MPM requires further evaluation.

- It is recommended to not use the level of pleural hyaluronic acid for the diagnosis of MPM, but further research on new soluble markers such as SMRP and osteopontin should be carried out in order to determine their role in the diagnosis of MPM (A).

**Question 2.1.7: What is the role of thoracoscopy in the diagnosis of MPM?**
Thoracoscopy is the best method to obtain the diagnosis of MPM when suspected on clinical or radiological data. Diagnostic accuracy is greater than 90% and complications occur in less than 10% of cases. Fibrohyaline pleural plaques are benign. In case of non-specific pleural lesions, biopsies should be performed on the parietal pleura around the plaques and in pleural zones "marked" by anthracosis.

- It is recommended, except in case of preoperative contraindication or pleural symphysis, to perform thoracoscopy for the diagnosis of MPM (A).

**Question 2.1.8: What is the role of thoracotomy procedure in the diagnosis of MPM?**
Direct access to the pleura by minimally invasive thoracotomy enables tissue biopsies to be obtained for pathological examination, notably in the absence of pleural effusion.

- This technique should be reserved for cases with potential pleural symphysis leading the failure of thoracoscopy procedure (A).

## 2.2. Pathological diagnostic criteria

The accurate diagnosis of mesothelioma, a malignant tumor which arises from mesothelial cells that line the serosal cavities, is made on histopathological examination. However, diagnosis can be extremely difficult because mesothelioma can show various misleading histopathological pitfalls, and pleura is a common site for metastatic disease.

Macroscopic appearance of mesothelioma depends of when in its natural history the tumor is first observed. As mesothelioma grows, the gross appearance is suggestive of MPM to some extent, although other malignant tumours (thymomas, carcinomas, lymphomas, angiosarcomas) can appear with a pseudomesotheliomatous aspect. The microscopic appearances of MPM are well defined in the international classification of pleural tumours.[11] However, this tumor has varied and deceptive appearance in a high percentage of cases and may resemble benign pleural lesions or metastatic lesions.

Pleural metastases are much more common than mesothelioma: 150 000 pleural metastatic lesions are recorded each year in the USA (compared with 1/~50 cases of mesothelioma). The most frequent primary cancers involving pleural metastatis are lung and breast carcinomas whose morphology can be mistaken for mesothelioma on standard sections stained with haematoxylin–eosin–saffron (in 7–15% and 7–11%, respectively).

Diagnostic problems also occur with benign inflammatory or reactive lesions of the pleura. These very frequent lesions occur often in patients of the same age group as mesothelioma (pleural effusion during cardiac failure, collagen disease, pneumonia or cirrhosis; they may lead to atypical mesothelial hyperplasia which can result in diagnostic error. In the French National Program of Mesothelioma Survey (1998–2007) experience, such errors represent 13% of initially diagnosed cases.

The quality of diagnosis will improve with time, due to a better understanding of the pathology by clinicians, particularly pneumonologists and pathologists, and progress in development of histopathological diagnostic techniques.

**Question 2.2.1: Which specimens for which clinical presentation?**

As pleural effusion is usually the first clinical sign of MPM, cytology is often the first diagnostic examination to be carried out.

- It is recommended to not make a diagnosis of mesothelioma based on cytology alone because of the high risk of diagnostic error (A).

Diagnosis of mesothelioma from fine needle biopsies (Abrams or Castelain needles) is associated with the same problems as cytology. A conclusive diagnosis can only be made if the material is representative of the tumor and in sufficient quantity to allow immunohistochemical characterisation.

- Fine needle biopsies are not recommended for the diagnosis of mesothelioma because they are associated with low sensitivity (around 30%). Thoracoscopy is preferred, allowing a diagnosis in more than 90% of cases (A).
- In the presence of fibrohyaline plaques, it is recommended that biopsies are taken from the edge of the plaque at the time of thoracoscopy (advice of experts).
- Faced with uniformly thick pleura, complete visual examination of the pleura is recommended, necessitating biopsies in the form of pleural scrapes (advice of experts).
- It is recommended that a diagnosis of MPM is not made on frozen tissue sections (A).

**Question 2.2.2: What classification should be used?**

- It is recommended that the WHO 2004 classification be used for mesothelial tumours, which provides a comparative basis for diagnosis, prognosis and patient management (A).

**Question 2.2.3: Should a complementary immunohistochemical examination be carried out in addition to morphological examination? If so, when? Which immunohistochemical markers should be used for which histological variants? How many antibodies should be used?**

- It is recommended that a diagnosis of MPM always be based on immunohistochemical examination (A).
- In full accordance withe the International Mesothelioma Panel, it is recommended to use two markers with positive diagnostic value for mesothelioma (nuclear markers such as anti-calretinin and anti-WT1 or the membrane marker anti-EMA, or for epithelioid mesothelioma, anti-CK5/6) and two markers with negative diagnostic value (anti-Ber-EP4, a membrane marker; anti-TTF1, a nuclear marker; monoclonal anti-CEA, anti-B72-3, anti-ER/PR, anti-EMA, cytoplasmic staining) to validate the diagnosis (A).
- For sarcomatoid forms, it is recommended to use two broad-spectrum anti-cytokeratin antibodies; negative immunostaining with a single antibody does not exclude the diagnosis (advice of experts), and two markers with negative predictive value (such as anti-CD34 and anti-BCL2, anti-desmin, anti-S100) to confirm the diagnosis (A).

For atypical mesothelial hyperplasia's (superficial mesothelial proliferations), there are currently no commercially available immunohistochemical markers which may indicate the benign or malignant nature of the cells.

**Question 2.2.4: Should electron microscopic examination be performed? When should this type of examination be performed?**

- Electron microscopy is a laborious examination and should not be routinely performed to confirm the diagnosis of mesothelioma. On the other hand, this technique is of value for epithelial tumours when immunohistochemical results are discordant, and in some sarcomatoid tumours. Moreover, it is not ultrastructurally

possible to reliably differentiate neoplastic from reactive mesothelial cells. The presence of long, thin microvilli is highly suggestive of mesothelioma (A).

**Question 2.2.5: What is the role of molecular biology? When should it be performed and what types of analysis are required? Should specimens need to be systematically frozen for a tissue bank?**

- There are no diagnostic or therapeutic reasons for freezing pleural tumor tissue. In contrast, it is recommended that tissue material should be frozen for research purposes, to increase our knowledge of this disease (predictive markers of progression, markers of resistance to chemotherapy, discovery of therapeutic targets) (A).

**Question 2.2.6: Should the advice of a panel of experts be sought faced with a suspicion of MPM?**

- It is recommended that a pathologists' panel (the ''Mesopath'' panel in France) is asked to confirm the diagnosis for patients included in randomised therapeutic trials, or in any case where there is doubt about the diagnosis (advice of experts).

## Question 3: What pre-therapeutic assessment should be proposed for a patient with MPM?

### Question 3.1: What assessment is necessary in a patient newly diagnosed with MPM at the time of initial management?

- It is recommended that a minimum assessment should include a clinical examination, a chest X-ray, a thoraco-abdominal CT scan with injection of contrast material (after removal of pleural fluid), a thoracoscopy with a standardised report, and a histopathological examination to precise the pathological subtype of MPM (A).
- For research purposes, this assessment should also include biological prognostic markers (SMRP, osteopontin) (B).

### Question 3.2: What additional non-invasive tests should be performed if an extrapleural pneumonectomy (EPP) is indicated?

- It is recommended that the pre-therapeutic assessment is completed with a chest MRI (facultative), a PET coupled with CT scan (PET-CT scan), a lung function study, a pulmonary scintigraphy, and a cardiac ultra-sound (B).

### Question 3.3: Which additional invasive examinations should be discussed before surgery if an EPP is indicated?

- Systematic contralateral thoracoscopy and laparoscopy are not recommended. An extent of MPM to the extrapleural lymph nodes is a contraindication for EPP. Mediastinoscopy is recommended if CT scan or PET suggest an extent to mediastinal lymph nodes (advice of experts).

### Question 3.4: Should talc pleurodesis be systematically performed at the time of thoracoscopy?

- It is recommended not to systematically perform talc pleurodesis at the time of diagnostic thoracoscopy. However, talc pleurodesis should be considered as part of the overall therapeutic plan proposed for the patient:
  - o If the subject is very old or if no active treatment is planned, talc pleurodesis should be performed (advice of experts).
  - o If EPP may be indicated for the stage of the disease, it is possible to perform talc pleurodesis if the operator is certain that this will not hinder recovery of biopsy samples for histological diagnosis. Thus, it is recommended not to perform talc pleurodesis if the macroscopic aspect of the pleura is not evocative of a malignant lesion, so that a second examination can be performed if necessary without being hampered by pleural symphysis (advice of experts).

### Question 3.5: How can the prognosis of a patient with MPM be evaluated? What is the value of prognostic factors in clinical practice?

The loco-regional extent of the disease is an important determinant of prognosis, with a significant survival benefit in case of early disease identified by thoracoscopy (stage Ia), or the absence of mediastinal lymph node invasion.

Besides the T and N criteria, other prognostic factors have been validated (CALGB/ EORTC), including demographic (sex, weight, age), clinical (performance status) or biological (histology, haemogram, inflammatory syndrome, LDH) variables.

Other prognostic factors have been reported that require further evaluation. These include tumor hypermetabolism measured by PET or biological markers such as SMRP.

- It is recommended that prognostic factors not be used on an individual level in daily practice. However, it is recommended that these prognostic factors are used in clinical research because they can contribute to the classification of patients into homogenous groups and facilitate comparison of results between studies (B).

### Question 3.6: How can the stage of MPM be determined? What are the limitations and disadvantages of the classifications currently available?

Since 1995, the International Mesothelioma Interest Group (IMIG) classification, based on CT Scan, is the most frequently used classification.

- Although the current classification has been only validated with patients who have been surgically treated, it is recommended to use the IMIG classification until a new system of classification better adapted to MPM has been set up (B).

## Question 4: What is the therapeutic strategy in MPM?

### Question 4.1: What is the role of surgery?

#### Question 4.1.1: What are the recommendations for surgery in MPM?

- A large postero-lateral thoracotomy usually through the 6th intercostal space is the recommended thoracic incision. The 6th rib can be resected to provide an adequate exposure (advice of experts).

*Pleurectomy* involves removal of the whole parietal, diaphragmatic and mediastinal pleura. Except in early stage of the disease (IA), pleurectomy is a palliative procedure.

- It is recommended that pleurectomy should not be performed in other disease stages than stage IA (advice of experts).

*Pleurectomy-decortication (P/D)* associates pleurectomy with visceral decortication, and entails resection of involved visceral pleural surface with preservation of lung parenchyma.

- P/D is considered as a palliative procedure. Therefore it is not a recommended surgical procedure for MPM (advice of experts).

*Extra-pleural pleuropneumonectomy (EPP)* includes the ''en-block'' removal of the pleura, pericardium, diaphragm, and the whole lung involved with the tumor. It is recommended to perform EPP by monoblock including resection of the diaphragmatic cupula for carcinological reasons.

- EPP is the only surgical procedure for MPM (except for stage IA) able to lead to a carcinological resection in selected patients, included in randomised clinical trials (advice of experts).

#### Question 4.1.2: What therapeutic strategy should be used for MPM?

- Regardless of the therapeutic strategy envisaged, surgical treatment of MPM should only be considered as part of a multidisciplinary approach to management (A).
- It is recommended that surgical treatment of MPM be performed in a reference centre able to offer both a surgical team trained in this kind of surgery and a pulmonary-oncologist medical team (A).

### Question 4.2: What is the role of chemotherapy?

#### Question 4.2.1: Has the benefit of chemotherapy been demonstrated?

First-line chemotherapy with a combination of cisplatin/pemetrexed or cisplatin/raltitrexed has been demonstrated to be more beneficial than monochemotherapy. No randomised study has demonstrated the benefit of second-line chemotherapy on survival or quality of life after failure of primary chemotherapy.

- It is recommended that patients in a good performance status (PS) be included in clinical trials, this approach being ethically acceptable (A).

#### Question 4.2.2: Which patients are likely to benefit from chemotherapy?

Patients older than 18 years of age, in a good PS (0 or 1) are likely to benefit from chemotherapy. The indications depend on comorbidities (cardiovascular, renal, pulmonary diseases) and the wishes of the patient and his family.

- The indication for chemotherapy should be discussed on a case-by-case basis in a multidisciplinary meeting (A).

#### Question 4.2.3: When should chemotherapy be started? For how long should chemotherapy be continued?

The available arguments in the literature, in favour of initiating chemotherapy as soon as a diagnosis is made, are weak and indirect.

- It is nevertheless recommended that administration of chemotherapy not be delayed and not to wait for the appearance of functional signs (C).
- It is recommended that chemotherapy be stopped in cases of progressive disease, grades 3–4 toxicities, or cumulative toxic doses (A), and after six cycles in patients who respond or are stable (C).

#### Question 4.2.4: What cytotoxic drugs are effective? As first-line treatment? As second-line treatment?

- The association of cisplatin and an antimetabolite (pemetrexed or raltitrexed) is recommended as first-line chemotherapy (A).
- No chemotherapy can be recommended as second-line after failure of chemotherapy including cisplatin. For patients who have not been given first-line treatment including cisplatin, cisplatin-based chemotherapy can be proposed (advice of experts).

#### Question 4.2.5: What is the role of biotherapies in the treatment of MPM?

- The role of immunomodulating agents is unknown and it is recommended that they not be used in the treatment of MPM outside clinical trials (A). Likewise, current data do not support intrapleural administration of immunomodulators outside clinical trials.
- To date, no targeted biotherapy has been demonstrated to be effective in MPM. It is recommended that trials be

continued with other molecules or other methods of administration (B).

**Question 4.2.6: What assessment criteria are used to determine the efficacy of these drugs?**

- It is recommended that overall survival be used as the primary outcome for evaluating the efficacy of chemotherapy in clinical trials (A).
- For assessment and follow-up of MPM, chest CT scan is recommended (A). When a patient has been treated for a pleural symphysis, it is recommended that chest CT scan be performed before the start of chemotherapy in order to better evaluate the response to chemotherapy (A).
- It is recommended that one of the following evaluation methods be used in clinical trials, depending on the appearance of the target lesion: WHO for bidimensional lesions, RECIST for unidimensional lesions, and modified RECIST in the case of circumferential pleural lesions (C).
- The role of PET or PET combined with CT scan in assessment of the response to chemotherapy requires evaluation; this approach means that a reference PET must be performed before any chemotherapy (C).

No biological marker has been validated to date for the evaluation of response to anti-tumor treatment in MPM.

- It is therefore recommended not to rely on the level of any one particular biological marker to evaluate treatment response (A).
- It is recommended that quality of life and symptoms during chemotherapy be evaluated to appreciate the clinical benefit (efficacy/tolerability) for diseases with a poor prognosis and for which the impact of treatment on survival has not been demonstrated clearly or is only marginal (A). No particular scale of quality of life is recommended on an individual level.

## Question 4.3: What is the role of radiotherapy in MPM?

**Question 4.3.1: What is the role of "palliative" radiotherapy aimed at pain relief?**

- Palliative radiotherapy aimed at pain relief is recommended in cases of painful parietal infiltration by MPM or subcutaneous metastasis (B).

**Question 4.3.2: What is the role of radiotherapy in the prevention of parietal seeding along the drainage channels?**

- It is recommended that irradiation with $3 \times 7$ Gy for three consecutive days, in the 4 weeks following drainage or thorascopy, be performed to prevent subcutaneous metastasis developing along drainage channels or thoracocentis tracts, using electrons with an energy adapted for depth (A) and a cutaneous bolus.
- To limit the risk of seeding along procedure tracts, it is recommended that pleural puncture be avoided, whenever possible, in cases where pleural effusion occurs in an individual known to be professionally exposed to asbestos. In those cases, primary thorascopy should be used in preference. Puncture points or thoracoscopic scars should be marked systematically for early irradiation as soon as the diagnosis is confirmed (advice of experts).

**Question 4.3.3: What is the role of post-operative radiotherapy?**

- Data from the literature are limited; however, it is not recommended that radiotherapy on large fields be performed after pleurectomy or decortication (C).
- In the absence of phase III randomised trials, the establishment of a prospective controlled study evaluating the efficacy and tolerability of adjuvant radiotherapy post-EPP (minimum dose of 50 Gy) is recommended (C).
- The technique of post-operative irradiation after EPP is complicated. It is therefore recommended to perform this in specialised centres (advice of experts).

**Question 4.3.4: What is the place for intensity-modulated radiotherapy (IMRT) in MPM after EPP?**
IMRT is of interest in this indication, but should be the subject of complementary studies.

- It is not recommended to use IMRT after EPP in MPM, outside clinical research studies (advice of experts).

## Question 4.4: Therapeutic indications for a multimodal approach to MPM.

**Question 4.4.1: What is the place for pleurectomy or pleurectomy/decortication (P/D)?**
In contrast to P/D, which is not recommended as it is not carcinologically valuable (see Question 4.1), pleurectomy has a role in the early stage of MPM (Ia). Nevertheless, comparative studies with other therapeutic strategies have not been done. This surgery is used at a stage of the disease when the natural history without treatment is unknown, and can be spontaneously long. It is difficult to realise a randomised clinical trial as this condition is very rare, making any recommendation impossible.

Likewise, in the more advanced stages, no randomised trial has compared decortication with EPP, or has evaluated the role of adjuvant treatment. No recommendation can therefore be given.

**Question 4.4.2: What is the place for extra-pleural pneumonectomy (EPP)?**

- It is recommended that EPP be performed in specialised centres used to this kind of radical surgery, as part of a multidisciplinary approach with adjuvant (radiotherapy) or neoadjuvant (chemotherapy) treatment (C).

It is not certain whether this 'radical' surgery, with a high morbidity and mortality, offers a survival benefit (on average 17 to 23 months). EPP can benefit only a select population (around 10% in total) for whom spontaneous survival is unknown in the absence of clinical trials comparing radical surgery with no surgery.

The feasibility of a multimodal approach should be proven (neoadjuvant chemotherapy with the reference protocol, cisplatin-pemetrexed) followed by EPP and post-operative radiotherapy (a single publication has reported the results of a pilot trial of 19 patients; several trials are currently underway). It is necessary to randomise patients to either surgery (MARS protocol in Great Britain) or radiotherapy (SAKK protocol in Switzerland) and chemotherapy. In addition to toxicity criteria (mortality and morbidity), it is necessary to evaluate quality of life.

- In the absence of results from these feasibility studies or randomised trials, it is recommended to perform this type of surgery only in clinical trials (A).

## Question 5: What methods are used to control symptoms and quality of life in MPM?

### Question 5.1: Management of pain

MPM is associated with pain initially due to excessive nociception. Much later in the disease process, neurogenic pain (neuropathological) may arise due to invasion of nervous structures or as a side effect of therapy.

**Question 5.1.1: How is pain in MPM evaluated?**
Chest pain is a frequent symptom of MPM. It becomes more and more disabling and refractory to analgesic treatment as the tumor growths. This is considered to be ''disease-pain''.

- In a patient able to communicate, a visual analogue scale is recommended to measure the evolution of cancer pain in MPM (A).
- In a patient who is confused and in pain due to progression of mesothelioma, a behavioural assessment analogous to the Doloplus scale can be used (C).

**Question 5.1.2: What are the general principles of treatment of nociceptive pain related to MPM?**
The World Health Organisation and various professional medical associations have established guidelines for cancer pain relief. Pain related to mesothelioma:

- Should be managed as cancer pain in general (B).
- Can be controlled in around 90% of cases by oral treatments. However, neurosurgical techniques can be performed, but decisions should be taken solely by a multidisciplinary team experienced in pain management in general and in these techniques in particular and after careful evaluation of the benefit/risk ratio for each indication (B).

### Question 5.2: Management of dyspnoea?

Dyspnoea is a common symptom in patients with MPM. In the majority of cases, dyspnoea is in relation with a pleural effusion, which is usually recurrent. Therefore, control of pleural effusion is the main treatment for dyspnoea in MPM.

**Question 5.2.1: Is repetition of pleural puncture for drainage justified?**
Repeated thoracentesis increase the risk of malignant seeding along of the puncture tracts, leading to the appearance of subcutaneous metastasis.

- It is recommended that repeated therapeutic thoracentesis not be performed in MPM, in order to avoid the repetition of prophylactic radiotherapy (advice of experts).

**Question 5.2.2: What is the place of talc pleurodesis?**

- Talc pleurodesis by thorascopy (talc poudrage) is the method of choice for the management of recurrent pleural effusion in a patient with MPM (B).
- Talc slurry is also an effective pleurodesis method. However, it is recommended that this technique is reserved for patients with poor performance status or with a limited life expectancy (advice of experts).

**Question 5.2.3: When should talc pleurodesis be performed?**

- It is recommended that talc pleurodesis is early performed, if it does not compromise the oncological therapeutic strategy (advice of experts).

**Question 5.2.4: Are other local treatments of value in the management of dyspnoea?**

- In case of failure of talc poudrage and for patients with poor performance status or with a limited life expectancy, insertion of a chronic indwelling pleural catheter is recommended (C).
- It is recommended that a pleuro-peritoneal shunt not be used because of the high risk of complications and the poor efficacy of this technique (C).

**Question 5.2.5: Do systemic anti-cancer treatments have an effect on dyspnoea?**

- The choice of chemotherapy can be based, at least in part, on the objective of relieving dyspnoea, insofar as this treatment can improve respiratory symptoms (C).

**Question 5.2.6: Can other measures be used to alleviate dyspnoea?**
No study has been performed to evaluate oxygen therapy in MPM. However, the prescription of long-duration oxygen therapy may be considered in current clinical practice in order to improve the comfort of a patient with hypoxaemia.

- As morphin-based analgesics have been shown to be effective in terms of improvement of dyspnoea, it is recommended that they be used preferentially in dyspnoeic patients with severe pain (advice of experts).
- In the absence of evidence, it is not recommended that systemic or inhaled corticotherapy be prescribed against dyspnoea (advice of experts).
- It is recommended that the emotional and psychological components of dyspnoea be systematically managed (advice of experts).

## Question 6: Medico-social aspects in MPM?

### Question 6.1: What medico-social approaches are possible?

In France, a diagnosis of MPM gives the patient a right to one or several medico-social benefits:

- Obtaining recognition of an occupational disease status, in the case of occupational asbestos exposure.
- Medical management with compensation from the ''Fonds d'Indemnisation des Victimes de l'Amiante (FIVA)'', a national compensation fund for victims of asbestos devoted to help patients with asbestos-related diseases, in addition or in replacement of a compensation for a recognised occupational exposure. For the FIVA, MPM is a disease considered as presumption of previous exposure to asbestos and therefore compensated.
- The right to benefit from early retirement (from the age of 50 years).

### Question 6.2: Why is a medico-social approach proposed?

A medico-social approach is appropriate because the diagnosis of MPM involves both collective and individual consequences and responsibilities.

### Question 6.3: How to proceed with different medico-social approaches?

Social services should be informed of an occupational disease by the patient provided with a medical certificate.

For MPM, it is important that an immunohistochemical analysis is available on pleural biopsies before requesting recognition of an occupational disease or when making a request for compensation from FIVA. In routine practice, it is desirable that cases are reassessed and confirmed histologically by a panel of pathology experts if there is any doubt about the diagnosis.

### Question 6.4: What is the role of the pulmonary physician in the medico-social field for a patient with MPM?

- In the case of probable or definite occupational exposure to asbestos identified by questioning, a medical certificate should be issued and given to the patient mentioning the disease and its possible link with previous occupational exposure (A).
- A request for compensation from FIVA should be proposed in France for all patients (or their eligible representatives), whether exposure to asbestos has been identified or not, and whatever the source of that exposure (A).

## Appendix. List of the French experts of the SPLF Conference on MPM

*Notice*: The full list of the references used by the experts may be found in: ''Recommandations de la Société de Pneumologie de Langue Française (SPLF) sur le Mésothéliome pleural—Conférence d'experts'' (full text). *Rev Mal Respir* 2006 (Special ed. in press). Copyright SPLF, Paris 2006, all rights reserved.

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